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Opioid reduction for patients with chronic pain in primary care: systematic review

Running head: Systematic review on opioid reduction

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Abstract

Background Long-term opioid treatment in patients with chronic pain is often ineffective and possibly harmful. These patients are often managed by general practitioners, who are calling for a clear overview of effective opioid reduction strategies for primary care. **Aim** Evaluate effectiveness of opioid reduction strategies applicable in primary care for patients with chronic pain on long-term opioid treatment. **Design** Systematic review of controlled trials and cohort studies. **Method** Literature search conducted in Embase, Medline, Web of Science, Cochrane CENTRAL register of trials, CINAHL, Google Scholar and PsychInfo. Studies evaluating opioid reduction interventions applicable in primary care among adults with long-term opioid treatment for chronic non-cancer pain were included. Risk of bias was assessed using Cochrane risk of bias (RoB) 2.0 tool or Risk-of-Bias in Non-randomized studies of Interventions (ROBINS-I) tool. Narrative synthesis was performed due to clinical heterogeneity in study designs and types of interventions. **Results** Five RCTs and five cohort studies were included (total n= 1717, range 35-985) exploring various opioid reduction strategies. Six studies had high RoB, three moderate RoB, and one low RoB. Three cohort studies investigating a GP supervised opioid taper (critical ROBINS-I), an integrative pain treatment (moderate ROBINS-I) and group medical visits (critical ROBINS-I) demonstrated significant between-group opioid reduction. **Conclusion** Results carefully point in the direction of a GP supervised tapering and multidisciplinary group therapeutic sessions to reduce long term opioid treatment. However, due to high risk of bias and small sample sizes, no firm conclusions can be made demonstrating need for more high-quality research. **Key words** Family practice, Opioid, Opioid Epidemic/prevention and control, Chronic pain, Patient care, Systematic review.

How this fits in

Though general practitioners are key players in tackling the opioid crisis, they feel ill equipped to reduce long-term opioid treatment in patients with chronic pain. This systematic review aimed to evaluate effectiveness of opioid reduction strategies for primary care. The results from this systematic review suggest that multidisciplinary and group-based interventions may be effective in reducing and discontinuing LTOT. However, due to high risk of bias and small sample sizes, no strong conclusions can be made demonstrating the need for more high-quality research in this field.

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Introduction

Where opioids once were the panacea to chronic non cancer pain (CNCP), today the negative effects of opioids are well-known. Short-term side effects of opioids include, among others, sedation and respiratory depression.[1] Opioids, also when prescribed by a doctor, are addictive in nature and may lead to tolerance, dependence and addiction.[2,3,4] Various observational studies suggest a dose-dependent association between long-term opioid treatment (LTOT) and an increased risk of myocardial infarction, fractures, falls and even all-cause mortality.[5,6] In addition, a growing amount of evidence indicates no difference in short-term effectiveness of opioid and non-opioid therapy for CNCP.[5] Research on long-term effectiveness of opioids on CNCP is still scarce, but limited available evidence suggest merely a weak effect of LTOT on pain relief in CNCP.[7,8, 9] Considering these serious harms and limited effectiveness, clinical guidelines on the management of CNCP no longer recommend opioid treatment. [8,10,11,12]

A key pillar to turn the tide on the opioid epidemic is to reduce LTOT in patients with CNCP. In the USA, the estimated prevalence of LTOT among patients with CNCP ranges between approximately 1 and 9%.[13] With waiting lists at addiction clinics and pain centers, GPs have by default become responsible to reduce LTOT. Yet, qualitative research among GPs report that GPs around the world feel ill-equipped to reduce opioids in these patients.[14,15] In other words, GPs playing a pivotal role in the opioid epidemic call for a clear overview of effective opioid reduction strategies which they can safely use in primary care.

Recently, three systematic reviews were published on effectiveness of opioid reduction strategies in CNCP.[16-18] Two of these reviews searched the literature up to 2017, whereas several trials were published in more recent years[19-24]. In addition, all three reviews looked at all available opioid reduction strategies and, thus, also included strategies that are not

applicable in primary care. This systematic review specifically aims at evaluating most recent evidence on effectiveness of opioid reduction strategies for CNCP on LTOT that are applicable in primary care.

Method

This systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[25] The review protocol was pre-registered in Prospero (CRD42021236399).

Data source and search strategy

The searches were carried out in Embase, Medline via Ovid, Web of Science Core Collection, Cochrane CENTRAL register of trials, CINAHL, Google Scholar and PsychInfo from inception date to 15th of January 2021 without restriction on language. Complete search strategy is presented in Supplementary Box 1. Backward citation tracking of eligible studies and backward snowballing of recent reviews[16-18] were performed.

Selection of studies

Two reviewers (LK, JRP) independently screened the articles by title and abstract using eligibility criteria presented in Table 1. All studies deemed eligible by at least one reviewer were read in full-text for eligibility by the same two reviewers. Where consensus between reviewers was not reached a third reviewer (BK) was consulted.

INCLUDE ABOUT HERE ----- Table 1: Eligibility criteria

Data extraction and risk of bias assessment

Study characteristics were extracted by one reviewer (LK) and checked by second reviewer (JRP). Outcome data were extracted independently by two reviewers (LK and JRP) using a standardized extraction form. Data extracted included, amongst others, intervention characteristics; comparison characteristics; primary outcome measures (mean opioid dose in mg Morphine Equivalent Daily Dose (MEDD) at baseline and end-of-intervention and/or mean opioid dose change) and secondary outcome measures (opioid discontinuation rates, incidence of adverse events, withdrawal symptoms, physical functioning, measures of mental well-being and overall quality of life). For cohort studies outcome data at last available time-point when still receiving the intervention was extracted and for studies that did not report outcome at end-of-intervention outcome data at next-available timepoint was extracted.

Two reviewers (LK and JRP) independently assessed risk of bias of included studies using Risk of Bias Tool 2.0 (RoB) for randomized controlled trials[26] and Risk-of-Bias in Non-randomized studies of Interventions tool (ROBINS-I) for non-randomized studies[27]. Disagreements between reviewers were solved by consensus.

Data synthesis

Due to substantial clinical heterogeneity in type of interventions and study designs, although a-priori planned, a meta-analysis was not possible and a narrative synthesis was adopted following the Synthesis Without Meta (SWiM) analysis guideline[28]. Effectiveness of interventions is presented as between-group differences and/or, if between-group differences were not available or if the outcome at baseline was significantly different between the groups, as within-group difference. Adjusted analysis correcting for baseline imbalances were presented if these resulted in a different conclusion.

Results

The search initially retrieved 10823 studies after removing duplicates. Of these, 106 studies were selected based on abstract and title and read in full-text. The corresponding authors of seven of these studies were contacted through mail because information on inclusion criteria was missing. All but one author responded to this mail. After review, 10 studies[19-24, 29-32] met the inclusion criteria and were included in this review (Figure 1).

INCLUDE ABOUT HERE ----- Figure 1: Prisma Flowchart -------

Study characteristics

The 10 included studies comprised 1717 (range 35-985) patients. Five studies[19,21,29,31,32] were randomized controlled trials (RCTs) and five studies[20,22,23,24,30] were cohort studies. A variety of opioid reduction methods from tapering protocols to alternative care strategies were explored. Supplementary Table 1 includes a summary of study and patient characteristics of included study.

Risk of bias

One RCT[29] had low risk of bias, two RCTs[19,32] had some concerns due to non-blinding of research participants and research staff, and the two remaining RCTs[21,31] had high risk of bias (Figure 2). One cohort studies[23] had moderate risk of bias. The remaining four studies[20,22,24,30] had a critical risk of bias (Figure 2). Complete ROB 2.0 and ROBINS-I assessments of the included cohort studies are presented in Supplementary Box 2 and 3.

INCLUDE ABOUT HERE ----- Figure 2: Schematic overview of ROB 2.0 and ROBINS-I assessments of included studies

Narrative summary of results

None of the included RCTs demonstrated a significant between-group difference in opioid dose. Three out of the five relatively small cohort studies[20,23,30], one with a moderate risk in bias (N=294) and two with a critical risk in bias (N= 84 and N=41), demonstrated a significant between-group difference in opioid reduction favoring the experimental intervention groups. The interventions researched by these cohort studies varied from a multidisciplinary pain treatment[23], group therapeutic sessions[30] to an individually tailored taper plan[20].

Narrative synthesis per study

A narrative synthesis of the included studies, primary outcomes and brief discussion of secondary outcomes is presented below. An overview and thorough explanation of outcomes is presented in Table 2.

INCLUDE ABOUT HERE ----- Table 2 Schematic overview of study results on primary and secondary outcomes

Description of results in RCTs

Liebschutz 2017[29]

In this cluster RCT (n=985), 1 year of TOPCARE intervention, consisting of nurse care management, electronic registry, academic detailing, and electronic decision tools was compared to 1 year of electronic decision tools only. There was no significant between-group difference in opioid dose at end-of-intervention (mean difference 6.5 mg MEDD, P=0.31). An adjusted regression analysis accounting for baseline imbalances demonstrated a statistically significant lower opioid use in the TOPCARE group, (mean difference (SE) 6.8 (1.6) mg MEDD, $p < 0.001$). Additionally, a non-statistically significant difference in opioid discontinuation among the groups was reported.

Garland 2020[19]

In this RCT (n=95), Mindfullness Oriented Recovery Enhancement (MORE) consisting of 8 weekly 2-hour mindfullness group sessions and daily 15-minute mindfulness practices at home was compared to active support group consisting in which the group sessions consisted of discussions on chronic pain and opioid reduction. In both groups there was no explicit call made to reduce opioid treatment. The study did not report on opioid dose at end-of-intervention, but at 1-month after intervention. The between-group mean difference was 110.6 mg MEDD in favor of the intervention (confidence intervals and p-values not provided). An intention-to-treat analysis using a linear mixed model with an interaction of group and time demonstrated a significant between group difference (p = 0.006).

Zgierska 2016[32]

In this RCT (n=35), patients were randomized to either Meditation-Cognitive Behavioural Therapy consisting 2-hour weekly group sessions and encouragement in formal mindfulness or usual care. At the end-of-the intervention period groups did not significantly differ in opioid dose change (mean change difference 5.7 mg MEDD, CI 95 % -34.3 – 45.7). Additionally, a significant between-group change in pain severity was reported in favor of the experimental intervention. There was no significant between-group difference in change in physical function nor in perceived stress.

Kurita 2018[21]

In this RCT (n = 35) all included participants were (if needed) switched to sustained release opioid therapy, after which they were randomized to either a taper-off intervention group or usual care. The intervention consisted of motivational talks and weekly or bi- weekly 10 % reduction of opioid dose until discontinuation. Due to a large drop-out, outcome assessments

were performed at 3.5 months. The mean between-group difference in opioid use was not significant (mean difference 74.2 mg MEDD, p=0,446). Additionally, the study reported no significant between-group difference in pain severity.

Sullivan 2017[31]

In this RCT (n = 35), participants interested in tapering their opioid dose were randomly assigned to either a taper support intervention or usual care. The intervention consisted of one visit with a physician followed by 17 weekly sessions in cognitive behavioral therapy for chronic pain with physician assistant followed by weekly dose reduction of 10 %. Between-group mean difference was 57.91 mg MEDD in favor of the taper support intervention (Confidence interval and p-value not reported). Adjusted analysis for baseline imbalances reported a non-significant between-group difference in MEDD (mean difference -42.9 mg MEDD, 95 % CI -92.42 - 6,62, p = 0,09) and pain severity.

Description of results in cohort studies

Seal 2020[23]

In this cohort study (n = 294) participants receiving consultations from an Integrated Pain Team consisting of primary care providers with training in pain management, pain pharmacists and pain psychologists were compared with participants receiving usual primary care. At 6 months mean between-group difference in opioid reduction was significant in favour of the experimental intervention (mean difference 38.7 mg MEDD, p < 0.03).

Vigil 2017[24]

In this cohort study (n = 66) participants enrolled in a Medical Cannabis Program were compared with participants that had declined the offer to enrol in the program. The difference

in opioid dose was non-statistically significant between groups (mean 0,1 mg, p = 0.974). The patients in cannabis program were significantly more likely to discontinue their opioid treatment.

Mehl-Madrona 2016[30]

In this cohort study (n = 84) participants attending Group Medical Visits (GMV) at least twice monthly in which non-pharmacological, Complementary and Alternative therapy were encouraged for the treatment of pain were matched with participants receiving usual care in same age decile, with same major diagnosis, same sex and within 25% in mg MEDD. At end-of-intervention (range 6 month – 2,5 years) a statistically significant mean between-group difference of 53.7 mg MEDD was reported in favor of the intervention (confidence interval and p-value were not reported). Additionally, a statistically significant difference in between-group discontinuation rate in favor of the intervention was reported. Differences in pain severity and quality of life were only reported for the intervention group, both demonstrating a statistically significant within-group change.

Montgomery 2020[22]

In this cohort study (n= 47) battlefield acupuncture a unique 5-point auricular acupuncture procedure was compared with usual care in patients on long-term opioid pain contract. The study reported a non-significant between-group mean difference of 18.85 mg MEDD (confidence interval and p-value not provided). Noteworthy, both groups increased opioid dose over the course of the study (mean difference BFA +3.9 mg MEDD, control + 8.7 mg MEDD, confidence intervals and p-values not provided). The study reported no significant difference in pain severity.

Goodman 2018[20]

In this cohort study (n= 41), patients had a conversation with their family physician (FP) discussing opioid cessation after which they could choose either an individually tailored opioid tapering by their FP or further pain treatment at a medial pain clinic. A significant between-group difference in opioid use in favour of the FP supervised tapering was reported (mean difference 118.26 mg MEDD, 95 % CI 23.23- 213.31mg MEDD, p= 0.018). However, the groups differed significantly in mean opioid dose at baseline with a higher opioid dose in the control group (mean difference 142.15 mg MEDD, 95 % CI 51.69-232.62 mg MEDD, p = 0.005). Within-group difference comparing opioid dose at baseline with opioid dose at end-of-intervention demonstrated a significant reduction in the FP supervised tapering group (mean difference 14.85 mg, 95 % CI 5.58 - 24.12, p=0.003) and a non-significant reduction in the control group (mean change 38.74 mg, 95% CI -42.88 - 120.368, p = 0.324).

Discussion

Summary

Five RCTS and five cohort studies were included in this systematic review. Studies were generally small and overall risk of bias was high. One RCT was graded low risk bias[29] (RoB 2 tool) but none of the cohort studies received this grading (ROBIN-S tool). There were some overarching principles explored; 5 studies[19,23,30,31,32] used psychological interventions as part of the intervention, 4 studies[19, 23,30,32] explored the effect of therapeutic group sessions and 3 studies[20,21,31] looked at opioid tapering. None of the RCTs demonstrated a significant between-group difference in opioid dose. Three out of the five cohort studies[20,23,30] demonstrated a significant between-group difference in opioid reduction favoring the experimental intervention groups.

Strengths and limitations

Conclusions of this systematic review are not without limitations. A comparison of study results was proposed by extracting between-group difference at end-of-intervention. However, in two studies[19,21] these results were not provided. In Kurita (2018)[21] due to loss of follow-up the extraction time point was brought forward, i.e. before end of intervention was reached, causing possible bias away from the null. Whereas, in Garland(2020)[19] the extraction time point is 10 weeks after intervention creating possible bias towards the null.

The generalizability of findings presented in this review to countries outside of the USA is limited, since all but one study was performed in the USA. One cannot simply assume that effectiveness of strategies for patients with CNCP on LTOT is the same all over the world, especially since the opioid crisis in the USA has found very different as compared with Europe and the rest of the world.[33] Moreover, to compare effectiveness equally and objectively among all included studies, 12 studies were excluded for not reporting on opioid dose reduction in MEDD. However, though excluded from this review, they might have reported on effective opioid reduction interventions. Finally, studies were excluded if they were considered not applicable in primary care which was up to the discretion of the first and second reviewer who based their opinion on types of strategies that would be applicable in the Netherlands and Denmark. Since primary care services vary from country to country, studies might have been included or excluded that could not or could have been implemented in primary care of other countries.

Comparison with existent literature

This systematic review included one RCT[19] that was not included in two most recent systematic reviews[17,18]. Additionally, four new cohort studies[20,22,23,24] were included, that were not included in most recent systematic review[16]. Hence, this review is to our knowledge the most

up-to-date review discussing intervention effectiveness of studies exploring opioid reduction strategies for patients with CNCP on LTOT applicable in primary care. Moreover, this is the first review that included only studies on opioid reduction strategies that are applicable in primary care.

Although this review specifically explored reduction strategies applicable in primary care the overall conclusion is in line with recent reviews[16-18], namely that no strong conclusions can be made regarding the benefit of opioid reduction strategies for people with CNCP due to overall high risks of bias and small sample sizes. With five new and recent studies identified[19,20,22,23,24], our review demonstrates a fast growth of studies exploring opioid reduction strategies.

Implications for research and practice

This review demonstrates the need for more high-quality research on opioid reduction strategies for patients with CNCP on LTOT. The fact that multiple research protocols for future research in this field were identified while scanning abstract and title[34-37] can be seen as a step in the right direction. These upcoming studies should build on lessons learned. Future research should include high-quality RCTs, where possible blinded for patients or at least for research personnel to reduce risks of bias. In addition, large drop-out rates, demonstrated by some included studies[19,21,30], can be expected and studies should opt for larger sample sizes than strictly needed to secure sufficient statistical power of end-results. In addition, it would be worthwhile for pilot trials to evaluate methods of retaining patients prior to performing large scale trials and to investigate, through qualitative evaluations, the reasons for patients to drop out. Moreover, to successfully evaluate a reduction strategy patient outcomes, such as pain severity and quality of life, should be assessed throughout the study to map the risks and benefits of opioid reduction strategies as these outcome measures are important topics in

patient-doctor conversations on reducing opioids.[16] Moreover, to increase generalizability of results, studies should be performed in more countries around the world.

Considering increasing waiting lists at pain clinics and rehabilitation centers, the positive outcome of Goodman[19] might inspire GPs to start with individually tailored opioid taper plans with patients that are receptive to that idea while taking the study's limitations into consideration. Likewise, results of Seal[23] and Mehl-Madrona[30] carefully points us in the direction of multidisciplinary group therapeutic sessions with a role for non-pharmacological pain treatments. High drop-out rates in some studies[19,21,30], suggest a need for close monitoring of patients when reducing their opioid treatment. Here, time is of the essence, something that is not always available in general practice. A role for nurse practitioners as was proposed by Liebschutz[29] might be a solution, however this will have to be investigated in more depth.

Conclusion

The results from this systematic review suggest that multidisciplinary and group-based interventions may be effective in reducing and discontinuing LTOT. However, due to high risk of bias and small sample sizes, no strong conclusions can be made demonstrating the need for more high-quality research in this field.

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Ethical approval

Not applicable

Competing interests

The authors have no competing interests to declare.

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Availability of data and material

Systematic review protocol is available at PROSPERO 2021 CRD42021236399 [Internet, available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021236399]. Extraction forms are available by contacting the corresponding author. Complete search strategy is available in the supplementary file, S1. The complete ROB 2.0 assessments and complete ROBINS-1 assessments are available in the supplementary files, S2 and S3.

Supplementary data

Supplementary Box S1: Complete search strategy

Supplementary Table S1: Summary of study and patient characteristics of included studies

Supplementary Box S2: Complete ROB 2.0 assessments of the included RCTs

Supplementary Box S3: Complete ROBINS-I assessments of the included cohort studies

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Figures:

Figure 1: Prisma Flowchart

Figure 2: Schematic overview of ROB 2.0 assessments of included RCTs

Table 1: Eligibility criteria
Inclusion criteria
Study is a Randomized Controlled Trial or Cohort study with control group
Study evaluates an intervention aimed to facilitate opioid dose reduction or discontinuation
Study is performed on patients 18 years or older
Study is performed on patients with Chronic Non-Cancer Pain, i.e. non-cancer pain lasting longer than 3 months
Study is performed receiving Long-Term Opioid Treatment prescribed by and legally obtained through a physician
Study is performed in primary care or intervention is applicable in primary care
Study reports on opioid reduction in mg Morphine Equivalent Daily Dose (MEDD)
Study is published and presented in full-text
Exclusion criteria
Study includes pregnant patients
Study includes patients with an oncological diagnosis
Study includes patients receiving palliative treatment
Study includes patients with acute or subacute pain, i.e. pain lasting shorter than 3 months
Study includes patients with opioid treatment shorter than 3 months

Table 2 : Schematic overview of study results on primary and secondary outcomes

Study	Study design	N (total)	Intervention vs. control	Risk of Bias[1]	Primary outcome	Secondary Outcomes			
					Opioid dose [2,3] mean difference (95% CI and/or p-value)	**Discontinuation rate[2]**	**Pain[2,3]**	**Physical function[2]**	**Mental wellbeing[2]**
Liebschutz, 2017	RCT	985	TOPCARE vs. Electronic decision tool	Low risk	6.5 (p=0.31)	-4,5% (p= 0.08)			
Garland, 2020	RCT	95	MORE vs. Active support group	Some concerns	110.6[4,5]				
Zgierska, 2016	RCT	35	Meditation-Cognitive behavioral Therapy vs. Usual care for CNCP	Some concerns	5.7 (95% CI -34.3-45.7)[6]		0.9 (95%CI 0.01-1.7)[6]	1.9, (95% CI -5.5 – 9.3)[6]	- 0.4 (95 % CI -5.2 – 4.4)[6]
Kurita, 2018	RCT	35	Taper off vs. Usual care	High risk	74.2 (p=0.446)[7]		-0,2 (p= 0.968)		
Sullivan, 2017	RCT	35	Tapper support intervention vs. Usual care	High risk	57.91[5,8]		0.68 (95 % CI 0.64-2.01, p = 0.30)[9]		
Seal 2020	Cohort	294	Integrative pain team treatment vs. Usual primary care	Moderate	38.7 mg (p=0.03)[10]				
Vigil 2017	Cohort	66	Medical Cannabis program vs. Usual care	Critical	- 0,1 mg (p=0.0974)	-37.1% (p < 0.001)			
Mehl-Madrona, 2016	Cohort	84	Group medical visit vs. Usual care	Critical	53.7[5,11]	-19% (p < 0.001)			
Montgomery, 2020	Cohort	47	Battlefield acupuncture vs. Usual care	Critical	18.85[5]		0 (p=0.15)		
Goodman, 2018	cohort	41	Individually tailored opioid taper vs. Treatment in medical pain clinic	Critical	118.26 (95%CI 23.23-213.31, p= 0.018)				

[1]RCTS were assessed using ROB 2.0 tool and cohort studies were assessed using ROBINS-I [2] Mean between-group difference comparing control to intervention group at end of intervention, unless stated differently [2] In mg of morphine equivalent daily dose (MEDD) [3] Pain severity on a Numeric rating scale (NRS), [4] Measured at 4 weeks after intervention was completed [5] P-values or confidence interval were not reported. [6]This value is a mean change difference comparing control to intervention,[7] Due to excessive drop-out rate data assessment was performed at 3,5 months follow-up,[8] In an adjusted analysis for baseline imbalances the mean between-group difference in MEDD was -42.9 mg (95 % CI -92.42 - 6,62, p = 0,09), [9] numbers based on the adjusted analysis for baseline imbalances, [10] Noteworthy, participants in the Integrative Pain Team group reported higher opioid misuse rates and were diagnosed more often with an opioid use disorder. In adjusted analysis controlling for these and other baseline imbalances using mixed-effects linear regression model the between-group difference remained significant with a mean between-group difference 38.2, 95% CI 13.0 – 63.5 mg, p < 0.01, [11]The within group differences comparing opioid dose at end-of-intervention to baseline were significant, mean difference intervention group - 49.7 mg MEDD, mean difference control group + 14.0 mg MEDD, both with p < 0,001. Note that, initially, 207 participants attended the intervention, yet the analysis of the intervention's effect was performed using the data of the 42 participants that had attended the intervention for at least six months.

Figure 1: PRISMA Flowchart

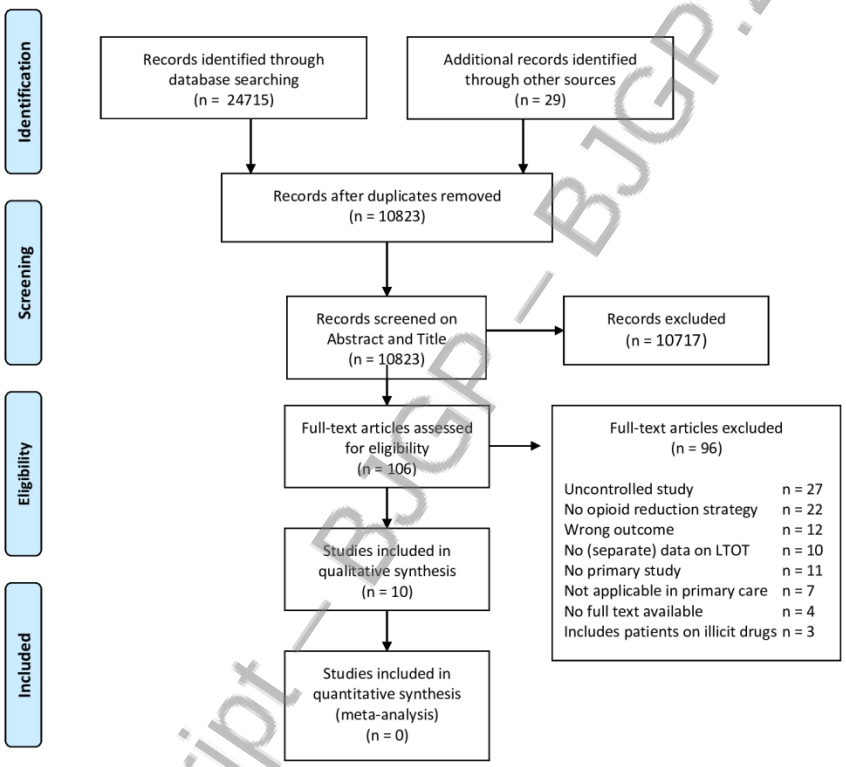

Figure 1: Prisma Flowchart

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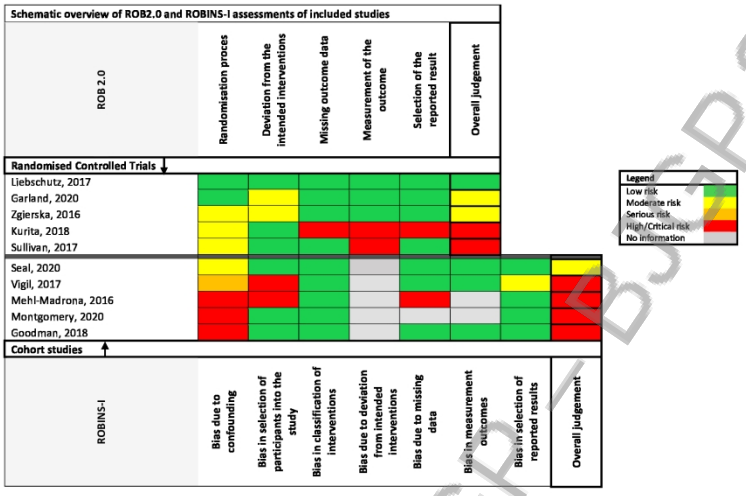

Figure 2: Schematic overview of ROB 2.0 and ROBINS-I assessments of included studies

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